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            $0.00    0.072 DialUnits File410
     $0.00  Estimated cost File410
     $0.46  TELNET
     $0.46  Estimated cost this search
     $0.46  Estimated total session cost   0.234 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2004/Jan W4
         (c) format only 2004 The Dialog Corp.
*File 155: Medline is updating again (12-22-2003).
Please see HELP NEWS 154, for details.
  File  55:Biosis Previews(R)  1993-2004/Jan W4
         (c) 2004 BIOSIS
  File  34:SciSearch(R) Cited Ref Sci  1990-2004/Jan W4
         (c) 2004 Inst for Sci Info
*File  34: New prices as of 1/1/2004 per Information Provider
request.  See HELP RATES 34.
  File 434:SciSearch(R) Cited Ref Sci  1974-1989/Dec
         (c) 1998 Inst for Sci Info
*File 434: New prices as of 1/1/2004 per Information Provider
request.  See HELP RATES434.
  File 340:CLAIMS(R)/US Patent  1950-04/Jan 29
         (c) 2004 IFI/CLAIMS(R)
*File 340: Annual reload and classification updates delayed due
 to processing issues.

      Set  Items  Description
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? s bad
      S1   31427  BAD
? s antibod?
      S2 1447854  ANTIBOD?
? s s1 and s2
           31427  S1
         1447854  S2
      S3     854  S1 AND S2
? s (bh1 or bh(w)1)
Processing
             362  BH1
            6321  BH
        11981737  1
              87  BH(W)1
      S4     444  (BH1 OR BH(W)1)
? s s3 and s4
             854  S3
             444  S4
      S5       2  S3 AND S4
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S6       2  RD (unique items)
? t s6/3,k,ab/1-2

 6/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

08448172   95136361   PMID: 7834748
   Bad ,  a heterodimeric partner for Bcl-XL and Bcl-2, displaces Bax
```

and promotes cell death.
Yang E; Zha J; Jockel J; Boise L H; Thompson C B; Korsmeyer S J
Howard Hughes Medical Institute, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110.
Cell (UNITED STATES) Jan 27 1995, 80 (2) p285-91, ISSN 0092-8674 Journal Code: 0413066
Contract/Grant No.: CA50239; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
To extend the mammalian cell death pathway, we screened for further Bcl-2 interacting proteins. Both yeast two-hybrid screening and lambda expression cloning identified a novel interacting protein, **Bad**, whose homology to Bcl-2 is limited to the **BH1** and BH2 domains. **Bad** selectively dimerized with Bcl-xL as well as Bcl-2, but not with Bax, Bcl-xs, Mcl-1, A1, or itself. **Bad** binds more strongly to Bcl-xL than Bcl-2 in mammalian cells, and it reversed the death repressor activity of Bcl-xL, but not that of Bcl-2. When **Bad** dimerized with Bcl-xL, Bax was displaced and apoptosis was restored. When approximately half of Bax was heterodimerized, death was inhibited. The susceptibility of a cell to a death signal is determined by these competing dimerizations in which levels of **Bad** influence the effectiveness of Bcl-2 versus Bcl-xL in repressing death.

Bad , a heterodimeric partner for Bcl-XL and Bcl-2, displaces Bax and promotes cell death.
... proteins. Both yeast two-hybrid screening and lambda expression cloning identified a novel interacting protein, **Bad**, whose homology to Bcl-2 is limited to the **BH1** and BH2 domains. **Bad** selectively dimerized with Bcl-xL as well as Bcl-2, but not with Bax, Bcl-xs, Mcl-1, A1, or itself. **Bad** binds more strongly to Bcl-xL than Bcl-2 in mammalian cells, and it reversed the death repressor activity of Bcl-xL, but not that of Bcl-2. When **Bad** dimerized with Bcl-xL, Bax was displaced and apoptosis was restored. When approximately half of...

...cell to a death signal is determined by these competing dimerizations in which levels of **Bad** influence the effectiveness of Bcl-2 versus Bcl-xL in repressing death.
; Amino Acid Sequence; **Antibodies**; Carrier Proteins--biosynthesis --BI; Carrier Proteins--chemistry--CH; Cloning, Molecular; Macromolecular Systems; Mammals; Mice; Molecular...
Gene Symbol: **bad**
Chemical Name: **Antibodies**; **Bad protein**; Carrier Proteins; Macromolecular Systems; Proto-Oncogene Proteins; Recombinant Proteins; bcl-x protein

6/3,K,AB/2 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3068935 IFI Acc No: 9838220
Document Type: C
BCL-X/BCL-2 ASSOCIATED CELL DEATH REGULATOR; IDENTIFYING AGENTS THAT INHIBIT BINDING OF POLYPEPTIDES
Inventors: Korsmeyer Stanley J (US)
Assignee: Washington University St Louis
Assignee Code: 90682
Publication (No,Date), Applic (No,Date):
US 5834209 19981110 US 96661479 19960610
Publication Kind: A
Calculated Expiration: 20130826
(Cited in 001 later patents)

Cont.-in-part Pub(No),Applic(No,Date): US 5691179 US 93112208 19930826; US 5700638 US 94248819 19940525
Division Pub(No),Applic(No,Date): US 5622852 US 94333565 19941031
Priority Applic(No,Date): US 96661479 19960610; US 93112208 19930826; US 94248819 19940525; US 94333565 19941031

Abstract: The invention provides a bcl-2 related protein, **Bad**, **Bad** muteins, two-hybrid systems comprising interacting **Bad** polypeptide sequences, **Bad** polynucleotides, and uses thereof.

Abstract: The invention provides a bcl-2 related protein, **Bad**, **Bad** muteins, two-hybrid systems comprising interacting **Bad** polypeptide sequences, **Bad** polynucleotides, and uses thereof.

Exemplary Claim: ...W I N G

1. A method for identifying agents that inhibit binding of a **Bad** polypeptide to a bcl-xL or bcl-2 polypeptide to form heteromultimers, said method comprising: performing a heterodimerization assay which includes a **Bad** polypeptide species comprising a **BH1** and BH2 domain with a bcl2 or bcl-xL polypeptide species and an agent under suitable binding conditions; determining whether the agent inhibits heterodimerization of the **Bad** polypeptide to the bcl-2 or bcl-xL polypeptide; identifying agents which inhibit said heterodimerization as candidate **Bad** modulating agents.

Non-exemplary Claims: 2. An isolated mammalian **BAD** polypeptide comprising an amino acid sequence which has at least 80% identity to SEQ ID NO:2, wherein the mammalian **BAD** polypeptide comprises a **BH1** domain and a BH2 domain and inhibits the death repressor activity of BCL-XL...

...3. The isolated mammalian **BAD** polypeptide of claim 2, wherein the amino acid sequence has at least 85% sequence identity...

...4. The mammalian **BAD** polypeptide of claim 3, wherein the amino acid sequence has at least 90% sequence identity...

...5. The mammalian **BAD** polypeptide of claim 4, wherein the amino acid sequence has at least 95% sequence identity...

...6. A hybrid protein comprising the mammalian **BAD** polypeptide of claim 2 and the activation domain or a DNA-binding domain of a...

...8. A composition comprising the **BAD** polypeptide of claim 2 and an isolated mammalian BCL-2 polypeptide or an isolated BCL...

...a fragment of said sequence or variant, wherein the polypeptide, variant or fragment comprises a **BH1** domain and a BH2 domain and inhibits the death repressor activity of BCL-XL...

...10. The polypeptide of claim 9, wherein the **BH1** domain is at least 90% identical to SEQ ID NO:10 and the BH2 domain...

...16. The **BAD** polypeptide of claim 9, further comprising an activation domain or a DNA-binding domain of...

...18. An isolated polypeptide comprising at least one **BAD** epitope of at least ten contiguous amino acids of SEQ ID NO:2 or a...

...none conservative amino acid substitution and wherein upon administration to a mammal the polypeptide generates **antibodies** specific for a naturally-occurring mammalian **BAD** polypeptide...

...19. The polypeptide of claim 18, wherein the **BAD** epitope comprises a conservatively substituted variant of SEQ ID NO:10, SEQ ID NO:17...

...20. The polypeptide of claim 41, wherein the **BAD** epitope comprises SEQ ID NO:10, SEQ ID NO:17, SEQ ID NO:18, SEQ...

?

0009667922 BIOSIS NO.: 199598135755
Bad, a Heterodimeric Partner for Bcl-X-L and Bcl-2, Displaces Bax and Promotes Cell Death
AUTHOR: Yang Elizabeth (Reprint); Zha Jiping; Jockel Jennifer; Boise Lawrence H; Thompson Craig B; Korsmeyer Stanley J
AUTHOR ADDRESS: Howard Hughes Med. Inst., Div. Mol. Oncol., Dep. Med., Washington University Sch. Med., St. Louis, MO 63110, USA**USA
JOURNAL: Cell 80 (2): p285-291 1995 1995
ISSN: 0092-8674
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To extend the mammalian cell death pathway, we screened for further Bcl-2 interacting proteins. Both yeast two-hybrid screening and lambda expression cloning identified a novel interacting protein, **Bad**, whose homology to Bcl-2 is limited to the **BH1** and **BH2** domains. **Bad** selectively dimerized with Bcl-x-L as well as Bcl-2, but not with Bax, Bcl-x-s, Mcl-1, A1, or itself. **Bad** binds more strongly to Bcl-x-L than Bcl-2 in mammalian cells, and it reversed the death repressor activity of Bcl-x-L, but not that of Bcl-2. When **Bad** dimerized with Bcl-x-L, Bax was displaced and apoptosis was restored. When approximately half of Bax was heterodimerized, death was inhibited. The susceptibility of a cell to a death signal is determined by these competing dimerizations in which levels of **Bad** influence the effectiveness of Bcl-2 versus Bcl-x-L in repressing death.

need ref:
"Bad" is
apoptosis in cell death

4/3,K,AB/16 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0012795551 BIOSIS NO.: 200000513864
Bcl-2 and apoptosis
AUTHOR: Russo F P (Reprint); Cinque B (Reprint); Cifone M G (Reprint)
AUTHOR ADDRESS: Dipartimento Medicina Sperimentale, Universita di L'Aquila, L'Aquila, Italy**Italy
JOURNAL: EOS-Rivista di Immunologia ed Immunofarmacologia 20 (1): p21-25 2000 2000
MEDIUM: print
ISSN: 0392-6699
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: Italian

ABSTRACT: The BCL-2 family, comprised of both pro-apoptotic and anti-apoptotic members, acts as a checkpoint upstream of Caspases and mitochondrial dysfunction. The death antagonists include Bcl-2, Bcl-XL, Mcl-1 and A1, whereas Bax, Bak, **Bad**, Bcl-Xs, Bcl-Xbeta and Bik are pro-apoptotic members. The overall ratio of the death agonists to antagonists determines the susceptibility to a death stimulus. Al members possess at least one of four conserved motifs known as Bcl-2 homology domains (**BH1** to BH4). These proteins are believed to be membrane bound and their ability to undergo both homodimerization and heterodimerization has been proposed to regulate apoptosis.

08762787 20043910 PMID: 10579309

Characterization of the antiapoptotic Bcl-2 family member myeloid cell leukemia-1 (Mcl-1) and the stimulation of its message by gonadotropins in the rat ovary.

Leo C P; Hsu S Y; Chun S Y; Bae H W; Hsueh A J

Department of Gynecology and Obstetrics, Stanford University Medical Center, California 94305-5317, USA.

Endocrinology (UNITED STATES) Dec 1999, 140 (12) p5469-77, ISSN 0013-7227 Journal Code: 0375040

Contract/Grant No.: HD-31566; HD; NICHD

Comment in Endocrinology. 1999 Dec;140(12) 5465-8; Comment in PMID 10579308

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The majority of ovarian follicles undergo atresia mediated by apoptosis. Bcl-2-related proteins act as regulators of apoptosis via the formation of dimers with proteins inside and outside the Bcl-2 family. Previous studies have identified **BAD** as a proapoptotic Bcl-2 family member expressed in the ovary. It is known that **BAD** phosphorylation induced by survival factors leads to its preferential binding to 14-3-3 and suppression of the death-inducing function of **BAD** . To identify ovarian binding partners for hypophosphorylated **BAD**, we performed a yeast two-hybrid screening of a rat ovary complementary DNA library using as bait a mutant **BAD** incapable of binding to 14-3-3. Screening of yeast transformants yielded positive clones encoding the rat ortholog of Mcl-1 (myeloid cell leukemia-1), an antiapoptotic Bcl-2 protein. Amino acid sequence analysis revealed that rat and human Mcl-1 showed a complete conservation of the Bcl-2 homology domains **BH1**, **BH2**, and BH3.
In the yeast two-hybrid system, Mcl-1 binds to the hypophosphorylated mutant of **BAD** and interacts preferentially with different proapoptotic (Bax, Bak, Bok, Bik, and BOD) compared with antiapoptotic Bcl-2 family members (Bcl-2, Bcl-xL, Bcl-w, Bfl-1, CED-9, and BHRF-1). Northern blot hybridization demonstrated expression of Mcl-1 transcri

4/3,K,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08947707 20237095 PMID: 10772918
Characterization of Bax-sigma, a cell death-inducing isoform of Bax.
Schmitt E; Paquet C; Beauchemin M; Dever-Bertrand J; Bertrand R
Research Centre of the University of Montreal Hospital Centre, Notre Dame Hospital, Montreal, Quebec, H2L 4M1, Canada.
Biochemical and biophysical research communications (UNITED STATES) Apr 21 2000, 270 (3) p868-79, ISSN 0006-291X Journal Code: 0372516
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The Ced-9/Bcl-like family of genes codes for proteins that have antiapoptotic and proapoptotic activity. Several Bax isoproteins have been detected by 2-D gel electrophoresis, and a novel human member, designated as Bax-sigma, has been identified and cloned from human cancer promyelocytic cells. Bax-sigma contains BH-3, **BH-1**, and **BH-2** domains, putative alpha-5 and alpha-6 helices, and the carboxy-terminal hydrophobic transmembrane domain but lacks amino acids 159 to 171 compared to Bax-alpha. mRNA expression analysis by reverse transcription-polymerase chain reaction and RNase protection assays have revealed that Bax-sigma is expressed in a variety of human cancer cell lines and normal tissues. To investigate the potential role of Bax-sigma in apoptosis, first its effects were compared to those of Bax-alpha by transient expression in human B lymphoma Namalwa cells. Both Bax-sigma and Bax-alpha promoted apoptosis, as detected by DNA fragmentation and morphological analysis by electron microscopy. The apoptosis induced by Bax-sigma and Bax-alpha was correlated with their expression, cytochrome c

08982570 20273610 PMID: 10816098

Role of the BH3 (Bcl-2 homology 3) domain in the regulation of apoptosis and Bcl-2-related proteins.

Lutz R J

Apoptosis Technology, Inc., Cambridge, MA 02139, USA.

Biochemical Society transactions (ENGLAND) Feb 2000, 28 (2) p51-6, ISSN 0300-5127 Journal Code: 7506897

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The Bcl-2 family of proteins play a prominent role in the regulation of apoptosis. From the initial identification of bcl-2 as an oncogene in follicular lymphoma through genetic studies in Caenorhabditis elegans to recent functional studies focusing on the importance of mitochondrial events in cell death signalling, the members of this protein family continue to be implicated in pivotal decision points regarding the survival of the cell. The family can be divided into two classes: those such as Bcl-2 and Bcl-xL that suppress cell death, and others, such as Bak and Bax, that appear to promote apoptosis. The Bcl-2 family is characterized by specific regions of homology termed Bcl-2 homology (**BH1**, **BH2**, BH3, BH4) domains, which are critical to the function of these proteins, including their impact on cell survival and their ability to interact with other family members and regulatory proteins. The identification of the BH3 domain as a potent mediator of cell death has led to the emergence of an additional family of proapoptotic proteins (such as **Bad**, Bik, Bid and Hrk) that share identity with Bcl-2 only within this death domain. These BH3-only proteins may be part of a regulatory network serving to integrate cell survival and death signals, an assertion that is supported by the identification of a BH3-only protein, Egl-1, as part of the central core of cell death signalling in C. elegans. While the mechanism of action of the BH3-only proteins remains unclear, recent studies on the regulation of critical protein-protein interactions and activity of **Bad** by phosphorylation in response to growth factor signalling suggest that the active state of BH3-only proteins may be regulated by post-translational modification. Additional modes of regulation, such as transcriptional,

10120786 22090453 PMID: 12095614

Direct addition of BimL to mitochondria does not lead to cytochrome c release.

Terradillos Olivier; Montessuit Sylvie; Huang David C S; Martinou Jean-Claude

Departement de Biologie Cellulaire, Sciences III, 30 quai E. Ansermet, 1211 Geneve 4, Switzerland.

FEBS letters (Netherlands) Jul 3 2002, 522 (1-3) p29-34, ISSN 0014-5793 Journal Code: 0155157

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Pro-apoptotic members of the Bcl-2 family can be subdivided in two classes according to their structure: a group including Bax, Bak, and Bok that display Bcl-2 homology (**BH**) **1**, **BH2** and BH3 domains and a second group including Bid (BH3 interacting domain death agonist), **Bad** , Bim (Bcl-2 interacting mediator of cell death) and several others that contain only a BH3 domain, the BH3-only proteins. The BH3-only proteins have been proposed to activate pro-apoptotic members of the Bax subfamily to trigger a mitochondrial pathway that leads to the release of cytochrome c and other apoptogenic factors. Here we report that the mechanism of action of Bim is different from that of Bid. Although overexpression of Bid or Bim in cells leads to cytochrome c release, only Bid is able to trigger the release of cytochrome c through Bax activation when added directly to isolated mitochondria. Bim(L), although unable to activate Bax, can directly inhibit Bcl-2 or Bcl-x(L). Our data suggest two functional classes of BH3-only proteins: those such as Bid which directly activate Bax-like proteins leading to mitochondrial membrane permeability and apoptosis and those such as Bim which inhibit anti-apoptotic proteins and render the cells more susceptible to apoptogenic stimuli.

... to their structure: a group including Bax, Bak, and Bok that display

11173157 98049404 PMID: 9389536

Expression and function of a proapoptotic Bcl-2 family member Bcl-XL/Bcl-2-associated death promoter (**BAD**) in rat ovary.

Kaipia A; Hsu S Y; Hsueh A J

Department of Gynecology and Obstetrics, Stanford University School of Medicine, California 94305-5317, USA.

Endocrinology (UNITED STATES) Dec 1997, 138 (12) p5497-504, ISSN 0013-7227 Journal Code: 0375040

Contract/Grant No.: HD 31566; HD; NICHD

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Bcl-2-related anti- and proapoptotic proteins are important in the decision step of the intracellular death program upstream from the caspase proteases. Targeted overexpression of Bcl-2 in ovarian somatic cells of transgenic mice leads to decreased apoptosis of granulosa cells and is associated with higher ovulation rate, increased litter size, and ovarian teratoma formation. The ability of exogenous Bcl-2 proteins to promote follicle cell survival suggests that the transgene can bind to endogenous ovarian Bcl-2 family members and modulate the intracellular apoptosis process in favor of cell survival. We used the yeast two-hybrid system to search for ovarian Bcl-2 interacting proteins. The screening of an ovarian fusion complementary DNA library yielded several clones encoding for the death agonist Bcl-XL/Bcl-2-associated death promoter (**BAD**). Dimerization of Bcl-2-related proteins mediated by the consensus Bcl-2 homology (BH) domains is essential for their apoptosis-regulating function. Consistent with these observations, yeast two-hybrid assays indicated that the interaction of Bcl-2 with **BAD** is dependent on both BH4 and **BH2** domains of Bcl-2. Northern blot analysis showed a wide distribution of **BAD** messenger RNA (mRNA) in diverse tissues with highest levels in the lung, ovary, uterus, and brain. In situ hybridization analysis indicated **BAD** mRNA expression in granulosa cells of different sizes of follicles and also in the theca and interstitial cells. **BAD** mRNA was expressed in the ovaries between postnatal 15-27 days and did not alter during the developmentally occurring apoptosis found about postnatal day 18 when the first group of early antral follicles were formed. Similarly, **BAD** mRNA levels did not change during follicle atresia induced by estrogen withdrawal in immature rats. To study the role of **BAD** in the ovary, **BAD** complementary DNA was transfected into primary cultures of granulosa cells and in a gonadal tumor cell line. Overexpression of **BAD** induced apoptosis in both cell types, and the effect of **BAD** was reversed by a membrane-permeable caspase inhibitor, indicating that **BAD** induces apoptosis via the activation of caspase cysteine proteases. In summary, the death agonist **BAD** was identified as a Bcl-2-interacting protein in the ovary, and **BAD** mRNA is constitutively expressed in granulosa cells, suggesting that **BAD** is an essential part of the ovarian cell death process. Because **BAD** overexpression in granulosa cells leads to apoptosis, future studies on ovarian **BAD** binding proteins and hormonal regulation of the interactions among different Bcl-2 family members could provide a better understanding of the cellular mechanism of ovarian follicle atresia.

...function of a proapoptotic Bcl-2 family member Bcl-XL/Bcl-2-associated death promoter (**BAD**) in rat ovary.

... yielded several clones encoding for the death agonist Bcl-XL/Bcl-2-associated death promoter (**BAD**). Dimerization of Bcl-2-related proteins mediated by the consensus Bcl-2 homology (BH) domains...

... with these observations, yeast two-hybrid assays indicated that the interaction of Bcl-2 with **BAD** is dependent on both BH4 and **BH2**

domains of Bcl-2. Northern blot analysis showed a wide distribution of **BAD** messenger RNA (mRNA) in diverse tissues with highest levels in the lung, ovary, uterus, and brain. In situ hybridization analysis indicated **BAD** mRNA expression in granulosa cells of different sizes of follicles and also in the theca and interstitial cells. **BAD** mRNA was expressed in the ovaries between postnatal 15-27 days and did not alter ...

... about postnatal day 18 when the first group of early antral follicles were formed. Similarly, **BAD** mRNA levels did not change during follicle atresia induced by estrogen withdrawal in immature rats. To study the role of **BAD** in the ovary, **BAD** complementary DNA was transfected into primary cultures of granulosa cells and in a gonadal tumor cell line. Overexpression of **BAD** induced apoptosis in both cell types, and the effect of **BAD** was reversed by a membrane-permeable caspase inhibitor, indicating that **BAD** induces apoptosis via the activation of caspase cysteine proteases. In summary, the death agonist **BAD** was identified as a Bcl-2-interacting protein in the ovary, and **BAD** mRNA is constitutively expressed in granulosa cells, suggesting that **BAD** is an essential part of the ovarian cell death process. Because **BAD** overexpression in granulosa cells leads to apoptosis, future studies on ovarian **BAD** binding proteins and hormonal regulation of the interactions among different Bcl-2 family members could ...

4/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10725904 97075341 PMID: 8917732
Importance of the Bcl-2 family in cell death regulation.

4/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11315314 98194755 PMID: 9535132

Cloning and expression of the programmed cell death regulator **Bad** in the rat brain.

D'Agata V; Magro G; Travali S; Musco S; Cavallaro S

Istituto di Bioimmagini e Fisiopatologia del Sistema Nervoso Centrale, Italian National Research Council, Catania.

Neuroscience letters (IRELAND) Feb 27 1998, 243 (1-3) p137-40, ISSN 0304-3940 Journal Code: 7600130

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The Bcl-2 family of proteins consists of both antagonists (e.g. Bcl-2) and agonists (e.g. Bax) that regulate apoptosis and compete through dimerization. In the present study we cloned the cDNA encoding the rat brain **BAD** , a distant member of the Bcl-2 family that was shown to promote cell death. The cloned cDNA encoded a protein of 205 amino acids, containing three putative Bcl-2 homology domains (**BH1**, **BH2** and BH3) and no C-terminal signal-anchor sequence. The predicted amino acid sequence was identical to the **Bad**-cDNA recently cloned from the rat ovary with the exception of a stretch of six amino acids, thus indicating the existence of two **Bad** alternative splice variants or a sequence artifact in the rat ovary **Bad**-cDNA. Immunohistochemical analysis in the rat brain revealed the exclusive expression of **Bad** in the epithelial cells of the choroid plexus, a result which is consistent with a very specialized function of **Bad** in the brain.

Cloning and expression of the programmed cell death regulator **Bad** in the rat brain.

... compete through dimerization. In the present study we cloned the cDNA

4/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11869450 99310955 PMID: 10381646

Survival activity of Bcl-2 homologs Bcl-w and A1 only partially correlates with their ability to bind pro-apoptotic family members.

Holmgreen S P; Huang D C; Adams J M; Cory S

The Walter and Eliza Hall Institute of Medical Research, PO Royal Melbourne Hospital Victoria 3050, Australia.

Cell death and differentiation (ENGLAND) Jun 1999, 6 (6) p525-32, ISSN 1350-9047 Journal Code: 9437445

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Certain Bcl-2 family members promote cell survival, whereas others promote apoptosis. To explore further how heterodimerization of opposing members affects survival activity, we have compared the abilities of the anti-apoptotic Bcl-w and A1 to bind to the pro-apoptotic Bax, Bak, **Bad** and Bik and to protect cells from their cytotoxic action. Bcl-w co-immunoprecipitated from cell lysates with Bax, Bak, **Bad** and Bik, but A1 bound only Bak and Bik. Mutation of A1 at a highly conserved glycine within the **BH1** domain prevented binding, but the comparable Bcl-w mutant still bound Bak, **Bad** and Bik, indicating that the glycine is not essential for all heterodimerization. Bcl-w and A1 protected against apoptosis induced by over-expression of Bax or **Bad** but not that induced by Bak or Bik. With several gene pairs, binding and protection were discordant. The results may reflect critical threshold affinities but also suggest that certain pro-apoptotic proteins may also contribute to apoptosis by a mechanism independent of binding pro-survival proteins.

...the anti-apoptotic Bcl-w and A1 to bind to the pro-apoptotic Bax, Bak,

```
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Processing
Processing
Processing
           6318  BH
       11977054  1
             86  BH(W)1
           6318  BH
       11222766  2
            190  BH(W)2
            362  BH1
            792  BH2
      S1    1171  BH(W)1 OR BH(W)2 OR BH1 OR BH2
? s bad
      S2   31422  BAD
? s s1 and s2
           1171  S1
          31422  S2
      S3      46  S1 AND S2
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>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
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      S4      21  RD (unique items)
? t s4/3,k,ab/1-21

 4/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

14455217   22412258   PMID: 12426317
  14-3-3  Interacts  directly  with  and negatively regulates pro-apoptotic
Bax.
  Nomura  Masaya;  Shimizu Shigeomi; Sugiyama Tomoyasu; Narita Masashi; Ito
Toshinori; Matsuda Hikaru; Tsujimoto Yoshihide
  Department  of Post-genomics & Diseases, Osaka University Graduate School
of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.
  Journal  of  biological chemistry (United States)   11 07 2002,  278  (3)
 p2058-65,  ISSN 0021-9258   Journal Code: 2985121R
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The  Bcl-2  family of proteins comprises well characterized regulators of
apoptosis,  consisting of anti-apoptotic members and pro-apoptotic members.
Pro-apoptotic  members  possessing  BH1,  BH2  , and BH3 domains
(such  as Bax and Bak) act as a gateway for a variety of apoptotic signals.
Bax is normally localized to the cytoplasm in an inactive form. In response
to  apoptotic  stimuli,  Bax translocates to the mitochondria and undergoes
oligomerization  to  induce  the  release  of  apoptogenic  factors such as
cytochrome  c,  but  it  is  still  largely  unknown  how the mitochondrial
translocation  and  pro-apoptotic  activity  of  Bax  is regulated. Here we
report  that  cytoplasmic  protein  14-3-3  theta  binds  to  Bax and, upon
apoptotic  stimulation, releases Bax by a caspase-independent mechanism, as
well  as  through  direct  cleavage  of  14-3-3  theta  by caspases. Unlike
Bad  ,  the  interaction  with  14-3-3  theta  is not dependent on the
phosphorylation  of  Bax.  In  isolated  mitochondria, we found that 14-3-3
theta  inhibited  the  integration  of  Bax  and  Bax-induced  cytochrome c
release.  Bax-induced  apoptosis  was inhibited by overexpression of either
14-3-3  theta  or  its  mutant (which lacked the ability to bind to various
phosphorylated  targets  but still bound to Bax), whereas overexpression of
```

14-3-3 theta was unable to inhibit apoptosis induced by a Bax mutant that did not bind to 14-3-3 theta. These findings indicate that 14-3-3 theta plays a crucial role in negatively regulating the activity of Bax.

... of apoptosis, consisting of anti-apoptotic members and pro-apoptotic members. Pro-apoptotic members possessing **BH1**, **BH2**, and BH3 domains (such as Bax and Bak) act as a gateway for a variety...

... mechanism, as well as through direct cleavage of 14-3-3 theta by caspases. Unlike **Bad** , the interaction with 14-3-3 theta is not dependent on the phosphorylation of Bax...

4/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11869450 99310955 PMID: 10381646
Survival activity of Bcl-2 homologs Bcl-w and A1 only partially correlates with their ability to bind pro-apoptotic family members.
Holmgreen S P; Huang D C; Adams J M; Cory S
The Walter and Eliza Hall Institute of Medical Research, PO Royal Melbourne Hospital Victoria 3050, Australia.
Cell death and differentiation (ENGLAND) Jun 1999, 6 (6) p525-32, ISSN 1350-9047 Journal Code: 9437445
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Certain Bcl-2 family members promote cell survival, whereas others promote apoptosis. To explore further how heterodimerization of opposing members affects survival activity, we have compared the abilities of the anti-apoptotic Bcl-w and A1 to bind to the pro-apoptotic Bax, Bak, **Bad** and Bik and to protect cells from their cytotoxic action. Bcl-w

Document Type: C
BCL-X/BCL-2 ASSOCIATED CELL DEATH REGULATOR; POLYNUCLEOTIDE COMPRISING SEQUENCE ENCODING MAMMALIAN BCL-XL/BCL-2 ASSOCIATED DEATH PROMOTER POLYPEPTIDE
Inventors: Korsmeyer Stanley J (US)
Assignee: Washington University St Louis
Assignee Code: 90682
Publication (No,Date), Applic (No,Date):
US 5622852 19970422 US 94333565 19941031
Publication Kind: A
Calculated Expiration: 20141031
(Cited in 004 later patents) Document Type: CERTIFICATE OF CORRECTION
Certificate of Correction Date: 19980825
Priority Applic(No,Date): US 94333565 19941031

Abstract: The invention provides a bcl-2 related protein, **Bad**, **Bad** muteins, two-hybrid systems comprising interacting **Bad** polypeptide sequences, **Bad** polynucleotides, and uses thereof.

Abstract: The invention provides a bcl-2 related protein, **Bad**, **Bad** muteins, two-hybrid systems comprising interacting **Bad** polypeptide sequences, **Bad** polynucleotides, and uses thereof.

Exemplary Claim: ...G

1. A polynucleotide, free of homologous chromosomal DNA, comprising a sequence encoding a mammalian **Bad** polypeptide, wherein said polypeptide a) lacks the carboxyl terminal signalanchor sequence characteristic of the membrane bound members of the bcl-2 family, b) has a **BH-1** and **BH-2** domain, and c) selectively heterodimerizes with bcl-2, and bcl-xL.

Non-exemplary Claims: 2. An isolated polynucleotide of claim 1, wherein said polynucleotide encodes **Bad** polypeptide of SEQ ID NO:2...

...7. A **Bad** polynucleolide encoding a **Bad** polypeptide of comprising SEQ ID NO:10 and SEQ ID NO:17...

9591926 21375766 PMID: 11483855

Underphosphorylated BAD interacts with diverse antiapoptotic Bcl-2 family proteins to regulate apoptosis.

Bae J; Hsu S Y; Leo C P; Zell K; Hsueh A J

Division of Reproductive Biology, Department of Gynecology and Obstetrics, Stanford University School of Medicine, Stanford, CA 94305-5317, USA.

Apoptosis - an international journal on programmed cell death (United States) Oct 2001, 6 (5) p319-30, ISSN 1360-8185 Journal Code: 9712129

Contract/Grant No.: HD31566; HD; NICHD

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Survival factors activate kinases which, in turn, phosphorylate the proapoptotic Bcl-xl/Bcl-2-associated death promoter homolog (BAD) protein at key serine residues. Phosphorylated BAD interacts with 14-3-3 proteins, and overexpression of 14-3-3 attenuates BAD-mediated apoptosis. Although BAD is known to interact with Bcl-2, Bcl-w, and Bcl-xL, the exact relationship between BAD and anti- or proapoptotic Bcl-2 proteins has not been analyzed systematically. Using the yeast two-hybrid protein interaction assay, we found that BAD interacted negligibly with proapoptotic Bcl-2 proteins. Even though wild type BAD only interacted with selected numbers of antiapoptotic proteins, underphosphorylated mutant BAD interacted with all antiapoptotic Bcl-2 proteins tested (Bcl-2, Bcl-w, Bcl-xL, Bfl-1/A1, Mcl-1, Ced-9, and BHRF-1). Using nonphosphorylated recombinant BAD expressed in bacteria, direct interactions between BAD and diverse antiapoptotic Bcl-2 members were also observed. Furthermore, apoptosis induced by BAD was blocked by coexpression with Bcl-2, Bcl-w, and Bfl-1. Comparison of **BAD** orthologs from zebrafish to **human** indicated the conservation of a 14-3-3 **binding** site and the BH3 **domain** during evolution. Thus, highly conserved BAD interacts with diverse antiapoptotic Bcl-2 members to regulate apoptosis.

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? s human(w)bad
Processing
Processing
        12625705  HUMAN
           31422  BAD
      S1      39  HUMAN(W)BAD
? s human(5n)bad
        12625705  HUMAN
           31422  BAD
      S2     201  HUMAN(5N)BAD
? s bh(w)1 or bh(w)2
Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing
            6318  BH
        11977054  1
              86  BH(W)1
            6318  BH
        11222766  2
             190  BH(W)2
      S3     264  BH(W)1 OR BH(W)2
? s s2 and s3
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             264  S3
      S4       3  S2 AND S3
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>>>Records from unsupported files will be retained in the RD set.
...completed examining records
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 5/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

08947707   20237095   PMID: 10772918
  Characterization of Bax-sigma, a cell death-inducing isoform of Bax.
  Schmitt E; Paquet C; Beauchemin M; Dever-Bertrand J; Bertrand R
  Research Centre of the University of Montreal Hospital Centre, Notre Dame
Hospital, Montreal, Quebec, H2L 4M1, Canada.
  Biochemical and biophysical research communications (UNITED STATES)   Apr
21 2000,  270  (3)  p868-79,  ISSN 0006-291X   Journal Code: 0372516
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The  Ced-9/Bcl-like  family  of  genes  codes  for  proteins  that  have
antiapoptotic  and proapoptotic activity. Several Bax isoproteins have been
detected  by  2-D gel electrophoresis, and a novel human member, designated
as  Bax-sigma,  has  been  identified  and  cloned  from  human  cancer
promyelocytic  cells.  Bax-sigma  contains  BH-3,  BH-1,  and
BH-2  domains,  putative  alpha-5  and alpha-6 helices, and the
carboxy-terminal hydrophobic transmembrane domain but lacks amino acids 159
to  171  compared  to  Bax-alpha.  mRNA  expression  analysis  by  reverse
transcription-polymerase  chain  reaction  and RNase protection assays have
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revealed that Bax-sigma is expressed in a variety of human cancer cell lines and normal tissues. To investigate the potential role of Bax-sigma in apoptosis, first its effects were compared to those of Bax-alpha by transient expression in human B lymphoma Namalwa cells. Both Bax-sigma and Bax-alpha promoted apoptosis, as detected by DNA fragmentation and morphological analysis by electron microscopy. The apoptosis induced by Bax-sigma and Bax-alpha was correlated with their expression, cytochrome c release, and caspase activation. In a yeast two-hybrid system, Bax-sigma interacted with several Ced-9/Bcl family members but had no affinity for the **human** Egl-1 homologs Bik and **Bad** and the Ced-4 homolog Apaf-1. In human cells, Bax-sigma function was counteracted by Bcl-xL overexpression, and co-immunoprecipitation experiments indicated that Bax-sigma was associated with Bcl-xL. Furthermore, Bax-sigma overexpression increased cell death induced by various concentrations of genotoxic agents with the most pronounced effect occurring at low camptothecin and vinblastine dose levels. Our results suggest that Bax-sigma, a novel variant of Bax, encodes a protein with a proapoptotic effect and mode of action similar to those of Bax-alpha. Copyright 2000 Academic Press.

... has been identified and cloned from human cancer promyelocytic cells. Bax-sigma contains BH-3, **BH-1**, and **BH-2** domains, putative alpha-5 and alpha-6 helices, and the carboxy-terminal hydrophobic transmembrane domain...
... sigma interacted with several Ced-9/Bcl family members but had no affinity for the **human** Egl-1 homologs Bik and **Bad** and the Ced-4 homolog Apaf-1. In human cells, Bax-sigma function was counteracted...
?

1/30/04

6445160 Genuine Article#: YT745 Number of References: 31
Title: Dimerization properties of **human BAD** - Identification of a BH-3 **domain** and analysis of its **binding** to mutant BCL-2 and BCL-X-L proteins (ABSTRACT AVAILABLE)
Author(s): Ottilie S; Diaz JL; Horne W; Chang J; Wang Y; Wilson G; Chang S; Weeks S; Fritz LC; Oltersdorf T (REPRINT)
Corporate Source: IDUN PHARMACEUT INC,11085 N TORREY PINES RD/LA JOLLA//CA/92037 (REPRINT); IDUN PHARMACEUT INC,/LA JOLLA//CA/92037
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1997, V272, N49 (DEC 5), P 30866-30872
ISSN: 0021-9258 Publication date: 19971205
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Abstract: Bad, an inducer of programmed cell death, was recently isolated from a mouse cDNA library by its ability to bind to the anti-apoptotic protein BCL-2. Sequence analysis suggested that Bad was a member of the BCL-2 gene family that encodes both inducers and inhibitors of programmed cell death. To further analyze the role of BAD in the network of homo- and heterodimers formed by the BCL-2 family, we have cloned the **human** homologue of **BAD** and assessed its biological activity and its interactions with wild type and mutant BCL-2 family proteins. Our results indicate that the **human BAD** protein, like its mouse homologue, is able to induce apoptosis when transfected into mammalian cells. Furthermore, in yeast two-hybrid assays as well as quantitative in vitro interaction assays, **human Bad** interacted with BCL-2 and BCL-X-L. Sequence alignments of **human BAD** revealed the presence of a BH-3 homology domain as seen in other BCL-2 family proteins, Peptides derived from this domain were able to completely inhibit the dimerization of BAD with BCL-X-L. Thus, as previously shown for BAX, BAK, BCL-2, and BCL-X-L, the BH3 domain of BAD is required for its dimerization with other BCL-2 family proteins. BAD was further analyzed for its ability to bind to various mutants of BCL-2 and BCL-X-L that have lost the ability to bind BAX and BAK, some of which retain biological activity and some of which do not. Surprisingly, all of the mutated BCL-2 and BCL-X-L proteins analyzed strongly interacted with

polyclonal / monoclonal epitopes

7/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07387408 92250600 PMID: 1374405
Localization of the protein 4.1-binding site on the cytoplasmic domain of erythrocyte membrane band 3.
Lombardo C R; Willardson B M; Low P S
Department of Chemistry, Purdue University, West Lafayette, Indiana 47907.
Journal of biological chemistry (UNITED STATES) May 15 1992, 267 (14) p9540-6, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: GM 24417; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Of the several proteins that bind along the cytoplasmic domain of erythrocyte membrane band 3, only the sites of interaction of proteins 4.1 and 4.2 remain to be at least partially localized. Using five independent techniques, we have undertaken to map and characterize the binding site of band 4.1 on band 3. First, transfer of a radioactive cross-linker (125I-2-(p-azido-salicylamido)ethyl-1-3-dithiopropionate) from purified band 4.1 to its binding sites on stripped inside-out erythrocyte membrane vesicles (stripped IOVs) revealed major labeling of band 3, glycophorin C, and glycophorin A. Proteolytic mapping of the stripped IOVs then demonstrated that the label on band 3 was confined largely to a fragment comprising residues 1-201. Second, competitive binding experiments with Fab fragments of monoclonal and peptide-specific **polyclonal antibodies** to **numerous epitopes** along the cytoplasmic domain of band 3 displayed stoichiometric competition only with Fabs to epitopes between residues 1 and 91 of band 3. Weak competition was also observed with Fabs to a sequence of the cytoplasmic domain directly adjacent to the membrane-spanning domain, but only at 50-100-fold excess of Fab. Third, band 4.1 protected band 3 from chymotryptic hydrolysis at tyrosine 46 and to a much lesser extent at a site within the junctional peptide connecting the membrane-spanning and cytoplasmic domains of band 3. Fourth, ankyrin, which has been previously shown to interact with band 3 both near a putative central hinge and at the N terminus competed with band 4.1 for band 3 in stripped IOVs. Since band 4.1 does not associate with band 3 near the flexible central hinge, the competition with ankyrin can be assumed to derive from a mutual association with the N terminus. Finally, a synthetic peptide corresponding to residues 1-15 of band 3 was found to mildly inhibit band 4.1 binding to stripped IOVs. Taken together, these data suggest that band 4.1 binds band 3 predominantly near the N terminus, with a possible secondary site near the junction of the cytoplasmic domain and the membrane.

... residues 1-201. Second, competitive binding experiments with Fab fragments of monoclonal and peptide-specific **polyclonal antibodies** to **numerous epitopes** along the cytoplasmic domain of band 3 displayed stoichiometric competition only with Fabs to epitopes...
?

10/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05088702 86089133 PMID: 2416941
Tubulin evolution: ciliate-specific epitopes are conserved in the ciliary tubulin of Metazoa.
Adoutte A; Claisse M; Maunoury R; Beisson J
Journal of molecular evolution (UNITED STATES) 1985, 22 (3) p220-9, ISSN 0022-2844 Journal Code: 0360051
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In spite of their overall evolutionary conservation, the tubulins of ciliates display electrophoretic and structural particularities. We show here that antibodies raised against Paramecium and Tetrahymena ciliary tubulins fail to recognize the cytoplasmic tubulins of all the metazoans tested. Immunoblotting of peptide maps of ciliate tubulins reveals that these antibodies react with one or very few ciliate-specific epitopes, in contrast to **polyclonal antibodies** against vertebrate tubulins, which are equivalent to autoantibodies and recognize **several epitopes** in both ciliate and vertebrate tubulins. Furthermore, we show that the anti-ciliate antibodies recognize ciliary and flagellar tubulins of metazoans ranging from sea urchin to mammals (with the exception of humans). The results support the conclusion that although duplication and specialization of tubulin genes in metazoans may have led to distinct types of tubulins, the axonemal one has remained highly conserved.

... that these antibodies react with one or very few ciliate-specific epitopes, in contrast to **polyclonal antibodies** against vertebrate tubulins, which are equivalent to autoantibodies and recognize **several epitopes** in both ciliate and vertebrate tubulins. Furthermore, we show that the anti-ciliate antibodies recognize...
?

10/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06036261 89051161 PMID: 2461231

Several epitopes of p85 glycoprotein (CDw44) are dependent on intact disulphide bonds. Isolation of cDNA clones requires a **polyclonal antibody** raised against the reduced protein.

Rogers I; D'Agostaro G; Vera S; Letarte M
Department of Immunology, University of Toronto.

Bioscience reports (ENGLAND) Aug 1988, 8 (4) p359-68, ISSN 0144-8463 Journal Code: 8102797
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Monoclonal antibodies 50B4 and 50E6 recognize two distinct epitopes of human p85 glycoprotein (CDw44). Both epitopes are destroyed by reduction of the purified glycoprotein as demonstrated by inhibition of cellular radioimmunoassay and Western blot analysis. Endoglycosidase F treated p85 glycoprotein, with an apparent molecular weight of 73,000, is still reactive with both monoclonal antibodies. Thus both epitopes are conformational determinants of the polypeptide chain. A rabbit antibody produced against purified native p85 glycoprotein also reacted only with the non-reduced form of p85. Repeated immunizations with SDS-dissociated and reduced p85 yielded a **polyclonal antibody** reactive by Western blot analysis with reduced and non-reduced forms of p85 glycoprotein. When a HOON leukemia cell line cDNA expression library was screened with this **polyclonal antibody**, two cDNA clones were isolated which reacted specifically with the antiserum and not with the control non-immune serum. Preliminary characterization of these clones indicates that they are p85-related.

10/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11463546 98347002 PMID: 9680484

The role of structure in antibody cross-reactivity between peptides and folded proteins.

Craig L; Sanschagrin P C; Rozek A; Lackie S; Kuhn L A; Scott J K
Institute of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, V5A 1S6, Canada.

Journal of molecular biology (ENGLAND) Aug 7 1998, 281 (1) p183-201, ISSN 0022-2836 Journal Code: 2985088R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Peptides have the potential for targeting vaccines against pre-specified epitopes on folded proteins. When **polyclonal antibodies** against native proteins are used to screen peptide libraries, most of the peptides isolated align to linear epitopes on the proteins. The mechanism of cross-reactivity is unclear; both structural mimicry by the peptide and induced fit of the epitope may occur. The most effective peptide mimics of protein epitopes are likely to be those that best mimic both the chemistry and the structure of epitopes. Our goal in this work has been to establish a strategy for characterizing epitopes on a folded protein that are candidates for structural mimicry by peptides. We investigated the chemical and structural bases of peptide-protein cross-reactivity using phage-displayed peptide libraries in combination with computational structural analysis. **Polyclonal antibodies** against the well-characterized antigens, hen eggwhite lysozyme and worm myohemerythrin, were used to screen a panel of phage-displayed peptide libraries. Most of the selected peptide sequences aligned to linear epitopes on the corresponding protein; the critical binding sequence of each epitope was revealed from these alignments. The structures of the critical sequences as they occur in other non-homologous proteins were analyzed using the Sequery and Superpositional Structural Assignment computer programs. These allowed us to evaluate the extent of conformational preference inherent in each sequence independent of its protein context, and thus to predict the peptides most likely to have structural preferences that match their protein epitopes. Evidence for sequences having a clear structural bias emerged for **several epitopes** , and synthetic peptides representing three of these epitopes bound antibody with sub-micromolar affinities. The strong preference for a type II beta-turn predicted for one peptide was confirmed by NMR and circular dichroism analyses. Our strategy for identifying conformationally biased epitope sequences provides a new approach to the design of epitope-targeted, peptide-based vaccines. Copyright 1998 Academic Press.

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10/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06036261 89051161 PMID: 2461231
Several epitopes of p85 glycoprotein (CDw44) are dependent on intact disulphide bonds. Isolation of cDNA clones requires a **polyclonal antibody** raised against the reduced protein.
Rogers I; D'Agostaro G; Vera S; Letarte M
Department of Immunology, University of Toronto.
Bioscience reports (ENGLAND) Aug 1988, 8 (4) p359-68, ISSN 0144-8463 Journal Code: 8102797
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
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Several epitopes of p85 glycoprotein (CDw44) are dependent on intact disulphide bonds. Isolation of cDNA clones requires a **polyclonal antibody** raised against the reduced protein.
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10/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05765113 88118607 PMID: 3123671
IL2-like material is present in human placenta and amnion.
Soubiran P; Zapitelli J P; Schaffar L
INSERM U210, Faculte de Medecine (Pasteur), Nice, France.
Journal of reproductive immunology (NETHERLANDS) Nov 1987, 12 (3) p225-34, ISSN 0165-0378 Journal Code: 8001906
Erratum in J Reprod Immunol 1988 Jun;13(1) 99
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human term placenta was shown to react with different polyclonal and monoclonal anti-interleukin 2 (IL2) antibodies by using indirect immunofluorescence on fro

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Set     Items   Description
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S2     165708   EPITOPE??
S3       4071   S1 AND S2
S4        120   NUMEROUS(5N)EPITOPE??
S5       4071   S1 AND S2
S6          7   S1 AND S4
S7          3   RD (unique items)
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        1418039  SEVERAL
         165708  EPITOPE??
      S8     284  SEVERAL(W)EPITOPE??
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            284  S8
      S9      8  S1 AND S8
? rd
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>>>Records from unsupported files will be retained in the RD set.
...completed examining records
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 10/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

11463546   98347002   PMID: 9680484
  The role of structure in antibody cross-reactivity between peptides and
folded proteins.
  Craig L; Sanschagrin P C; Rozek A; Lackie S; Kuhn L A; Scott J K
  Institute of Molecular Biology and Biochemistry, Simon Fraser University,
Burnaby, BC, V5A 1S6, Canada.
  Journal of molecular biology (ENGLAND)  Aug 7 1998,  281  (1)  p183-201,
ISSN 0022-2836   Journal Code: 2985088R
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Peptides have the potential for targeting vaccines against pre-specified
epitopes on folded proteins. When polyclonal antibodies against
native proteins are used to screen peptide libraries, most of the peptides
isolated align to linear epitopes on the proteins. The mechanism of
cross-reactivity is unclear; both structural mimicry by the peptide and
induced fit of the epitope may occur. The most effective peptide mimics of
protein epitopes are likely to be those that best mimic both the chemistry
and the structure of epitopes. Our goal in this work has been to establish
a strategy for characterizing epitopes on a folded protein that are
candidates for structural mimicry by peptides. We investigated the chemical
and structural bases of peptide-protein cross-reactivity using
phage-displayed peptide libraries in combination with computational
structural analysis. Polyclonal antibodies against the
well-characterized antigens, hen eggwhite lysozyme and worm myohemerythrin,
were used to screen a panel of phage-displayed peptide libraries. Most of
the selected peptide sequences aligned to linear epitopes on the
corresponding protein; the critical binding sequence of each epitope was
revealed from these alignments. The structures of the critical sequences as
they occur in other non-homologous proteins were analyzed using the Sequery
and Superpositional Structural Assignment computer programs. These allowed
us to evaluate the extent of conformational preference inherent in each
sequence independent of its protein context, and thus to predict the
```

peptides most likely to have structural preferences that match their protein epitopes. Evidence for sequences having a clear structural bias emerged for **several epitopes** , and synthetic peptides representing three of these epitopes bound antibody with sub-micromolar affinities. The strong preference for a type II beta-turn predicted for one peptide was confirmed by NMR and circular dichroism analyses. Our strategy for identifying conformationally biased epitope sequences provides a new approach to the design of epitope-targeted, peptide-based vaccines. Copyright 1998 Academic Press.

Peptides have the potential for targeting vaccines against pre-specified epitopes on folded proteins. When **polyclonal antibodies** against native proteins are used to screen peptide libraries, most of the peptides isolated align...

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10/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06036261 89051161 PMID: 2461231

Several epitopes of p85 glycoprotein (CDw44) are dependent on intact disulphide bonds. Isolation of cDNA clones requires a **polyclonal antibody** raised against the reduced protein.

Rogers I; D'Agostaro G; Vera S; Letarte M

8913905 20201547 PMID: 10738968

Unraveling distinct intracellular signals that promote survival and proliferation: study of erythropoietin, stem cell factor, and constitutive signaling in leukemic cells.

Sawyer S T; Jacobs-Helber S M

Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0613, USA.

Journal of hematotherapy & stem cell research (UNITED STATES) Feb 2000, 9 (1) p21-9, ISSN 1525-8165 Journal Code: 100892915

Contract/Grant No.: RO1DK39781; DK; NIDDK

Document type: Journal Article; Review; Review Literature

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

This **review** summarizes selected recent studies of the intracellular signals that allow erythroid cells to survive and proliferate under the control of erythropoietin (EPO) and alteration in signals that contribute to EPO-independent survival and proliferation. The hypothesis explored is that the proliferation and survival signals are distinct and can be separately studied with the proper cell lines and growth factor stimulation. The anti- and pro-apoptotic proteins **Bcl**-XL and **BAD** are highly implicated in EPO-dependent survival of erythroid cells. Stat5 activity appears to be upstream of **Bcl**-XL expression such that pathologic, constitutive activation of Stat5 may be a common event in leukemic cells that become resistant to **apoptosis** by constitutive expression of **Bcl** -XL. Other signals apparently also control the expression of **Bcl** -XL, such as the expression of JunB which seem to be required to suppress **Bcl**-XL expression when EPO is withdrawn. **Apoptosis** may also be triggered by inactivation of **Bcl**-XL by **BAD**. Dephosphorylation of **BAD** as a result of withdrawal of survival factors converts prosurvival **BAD** to proapoptotic **BAD**. Phosphorylation of **BAD** at the serine 112 residue seems critical to promoting survival. Constitutive activation of a kinase that phosphorylates **BAD** serine 112 may, therefore, contribute to resistance to **apoptosis** in leukemic cells. We describe the resistance of erythroleukemic cells to **apoptosis** induced by EPO withdrawal apparently caused by constitutive **BAD** phosphorylation. The resistance to **apoptosis** in these cells is reversed by treatment with the PI3-kinase inhibitor, LY294002, suggesting that resistance to **apoptosis** in these cells likely results from constitutive P13-kinase that is an upstream activator of an S-112 **BAD** kinase. The MAP kinase cascade is apparently active in EPO-dependent and stem cell factor (SCF)-dependent proliferation but not survival. In addition, autocrine tumor necrosis factor-a! (TNF-alpha) may also be a proliferation factor not affecting survival. P13-kinase seems to be required for full EPO-dependent proliferation but is not required for EPO-dependent survival (but it can promote survival when activated).

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Constitutive activation of a kinase that phosphorylates **BAD** serine 112 may, therefore, contribute to resistance to **apoptosis** in leukemic cells. We describe the resistance of erythroleukemic cells to **apoptosis** induced by EPO withdrawal apparently caused by constitutive **BAD** phosphorylation. The resistance to **apoptosis** in these cells is reversed by treatment with the PI3-kinase inhibitor, LY294002, suggesting that resistance to **apoptosis** in these cells likely results from constitutive P13-kinase that is an upstream activator of an S-112 **BAD** kinase. The MAP kinase cascade is apparently active in EPO-dependent and stem cell factor...

8/3,K,AB/10 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0014385008 BIOSIS NO.: 200300341751

8/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09484391 21260650 PMID: 11368354
Phosphorylation of **Bcl2** and regulation of **apoptosis**.
Ruvolo P P; Deng X; May W S
University of Florida Shands Cancer Center and Department of Medicine, Gainesville 32610-0232, USA.
Leukemia - official journal of the Leukemia Society of America, Leukemia Research Fund, U.K (England) Apr 2001, 15 (4) p515-22, ISSN 0887-6924 Journal Code: 8704895
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Members of the **Bcl2** family of proteins are important regulators of programmed cell death pathways with individual members that can suppress (eg **Bcl2**, **Bcl**-XL) or promote (eg Bax, **Bad**) **apoptosis**. While the mechanism(s) of **Bcl2**'s anti-apoptotic function is not yet clear, introduction of **Bcl2** into most eukaryotic cell types will protect the recipient cell from a wide variety of stress applications that lead to cell death. There are, however, physiologic situations in which **Bcl2** expression apparently fails to protect cells from **apoptosis** (eg negative selection of thymocytes). Further, **Bcl2** expression in patient tumor samples does not consistently correlate with a worse outcome or resistance to anticancer therapies. For example, patient response and survival following chemotherapy is independent of **Bcl2** expression at least for pediatric patients with ALL. These findings indicate that simple expression of **Bcl2** may not be enough to functionally protect cells from **apoptosis**. The finding that **Bcl2** is post-translationally modified by phosphorylation suggests another level of regulation of function. Recent studies have shown that agonist-activated phosphorylation of **Bcl2** at serine 70 (single site phosphorylation), a site within the flexible loop domain (FLD), is required for **Bcl2**'s full and potent anti-apoptotic function, at least in murine IL-3-dependent myeloid cell lines. Several protein kinases have now been demonstrated to be physiologic **Bcl2** kinases indicating the importance of this post-translational modification. Since **Bcl2** phosphorylation has been found to be a dynamic process involving both a **Bcl2** kinase(s) and phosphatase(s), a mechanism exists to rapidly and reversibly regulate **Bcl2** 's activity and affect cell viability. In addition, multisite **Bcl2** phosphorylation induced by anti-mitotic drugs like paclitaxel may inhibit **Bcl2** indicating the potential wide range of functional consequences that this post-translational modification may have on function. While post-translational mechanisms other than phosphorylation may also regulate **Bcl2** 's function (eg ubiquitination), this **review** will focus on the regulatory role for phosphorylation and discuss its potential clinical ramifications.

Phosphorylation of **Bcl2** and regulation of **apoptosis**.
Members of the **Bcl2** family of proteins are important regulators of programmed cell death pathways with individual members that can suppress (eg **Bcl2**, **Bcl**-XL) or promote (eg Bax, **Bad**) **apoptosis**. While the mechanism(s) of **Bcl2**'s anti-apoptotic function is not yet clear, introduction of **Bcl2** into most eukaryotic cell types will protect the recipient cell from a wide variety of stress applications that lead to cell death. There are, however, physiologic situations in which **Bcl2** expression apparently fails to protect cells from **apoptosis** (eg negative selection of thymocytes). Further, **Bcl2** expression in patient tumor samples does not consistently correlate with a worse outcome or resistance to anticancer therapies. For example, patient response and survival following chemotherapy is independent of **Bcl2** expression at least for pediatric patients with

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Descriptors: **Apoptosis**; *Proto-Oncogene Proteins c-**bcl**-2 --metabolism--ME

10033464 21969217 PMID: 11973609

Keeping killers on a tight leash: transcriptional and post-translational control of the pro-apoptotic activity of BH3-only proteins.

Puthalakath H; Strasser A

The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.

Cell death and differentiation (England) May 2002, 9 (5) p505-12, ISSN 1350-9047 Journal Code: 9437445

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BH3-only proteins are structurally distant members of the **Bcl**-2 protein family that trigger **apoptosis**. Genetic experiments have shown that these proteins are essential initiators of programmed cell death in species as distantly related as mice and C. elegans. BH3-only proteins share with each other and with the remainder of the **Bcl**-2 family only a nine amino acid BH3 (**Bcl**-2 Homology) region. Mutational analyses have demonstrated that this domain is required for their ability to bind to **Bcl**-2-like pro-survival proteins and to initiate **apoptosis**. So far only one BH3-only protein, EGL-1, has been identified in C. elegans and it is required for all developmentally programmed death of somatic cells in this species. In contrast, mammals have at least 10 BH3-only proteins that differ in their expression pattern and mode of activation. Studies in gene targeted mice have indicated that different BH3-only proteins are required for the initiation of distinct apoptotic stimuli. The pro-apoptotic activities of BH3-only proteins are stringently controlled by a variety of mechanisms. C. elegans egl-1 as well as mammalian hrk/dp5, noxa, puma/bbc3 and bim/bod are regulated by a diverse range of transcription factors. Certain BH3-only proteins, including **Bad**, Bik/Nbk, Bid, Bim/Bod and Bmf, are restrained by post-translational modifications that cause their sequestration from pro-survival **Bcl**-2 family members. In this **review** we describe current knowledge of the functions and transcriptional as well as post-translational control mechanisms of

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  File 155:MEDLINE(R)  1966-2004/Jan W4
         (c) format only 2004 The Dialog Corp.
*File 155: Medline is updating again (12-22-2003).
Please see HELP NEWS 154, for details.
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*File 340: Annual reload and classification updates delayed due
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          274274  S2
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? s bcl?
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           68429  S4
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 8/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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16046056   PMID: 14613034
   Targeting Bcl-2 and Bcl-XL with nonpeptidic small-molecule
antagonists.
  Wang Shaomeng; Yang Dajun; Lippman Marc E
  Department of Internal Medicine and Comprehensive Cancer Center,
University of Michigan Medical School, Ann Arbor, MI 48109, USA.
  Seminars in oncology (United States)  Oct 2003, 30 (5 Suppl 16)
 p133-42,  ISSN 0093-7754   Journal Code: 0420432
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Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
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Members of the **Bcl**-2 family of proteins are crucial regulators of programmed cell death or **apoptosis** . This family of proteins now includes both anti-apoptotic molecules such as **Bcl**-2 and **Bcl** -X(L), and pro-apoptotic molecules such as Bax, Bak, Bid, and **Bad**. The majority of human cancers are found to have overexpression of **Bcl** -2, **Bcl**-X(L), or both. **Bcl**-2 and **Bcl**-X(L) may play a critical role in cancer progression. Cancers with high levels of **Bcl** -2 or **Bcl**-X(L) or both proteins are resistant to a wide spectrum of chemotherapeutic agents and radiation therapy. **Bcl**-2 and **Bcl** -X(L) have become attractive targets for designing new anticancer drugs. Small-molecule inhibitors that are capable of inhibiting the activity of **Bcl**-2 and **Bcl**-X(L) may have great therapeutic potential as an entirely new class of anticancer drugs for treating many forms of cancers in which **Bcl**-2 and/or **Bcl**-X(L) proteins are overexpressed and for which traditional therapies are ineffective. Design of small-molecule inhibitors of **Bcl**-2 and **Bcl**-X(L) is a very new and exciting area for current anticancer drug design and development. In this article we will provide a brief **review** on the strategy and recent progress in designing small-molecule antagonists targeting **Bcl**-2 and **Bcl** -X(L).

Targeting **Bcl**-2 and **Bcl**-XL with nonpeptidic small-molecule antagonists.

Members of the **Bcl**-2 family of proteins are crucial regulators of programmed cell death or **apoptosis** . This family of proteins now includes both anti-apoptotic molecules such as **Bcl**-2 and **Bcl** -X(L), and pro-apoptotic molecules such as Bax, Bak, Bid, and **Bad**. The majority of human cancers are found to have overexpression of **Bcl** -2, **Bcl**-X(L), or both. **Bcl**-2 and **Bcl**-X(L) may play a critical role in cancer progression. Cancers with high levels of **Bcl** -2 or **Bcl**-X(L) or both proteins are resistant to a wide spectrum of chemotherapeutic agents and radiation therapy. **Bcl**-2 and **Bcl** -X(L) have become attractive targets for designing new anticancer drugs. Small-molecule inhibitors that are capable of inhibiting the activity of **Bcl**-2 and **Bcl**-X(L) may have great therapeutic potential as an entirely new class of anticancer drugs for treating many forms of cancers in which **Bcl**-2 and/or **Bcl**-X(L) proteins are overexpressed and for which traditional therapies are ineffective. Design of small-molecule inhibitors of **Bcl**-2 and **Bcl**-X(L) is a very new and exciting area for current anticancer drug design and development. In this article we will provide a brief **review** on the strategy and recent progress in designing small-molecule antagonists targeting **Bcl**-2 and **Bcl** -X(L).

Descriptors: Antineoplastic Agents--pharmacology--P